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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,400	02/26/2002	Hans-Rainer Hoffmann	3868-0109P	3239

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EXAMINER	
MAIER, LEIGH C	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,400	HOFFMANN ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) 1-13 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 14-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/26/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group II in the response dated November 4, 2003 is acknowledged. The traversal is on the ground that the composition of Group I and the method of making the composition of Group II are so intimately interrelated that no undue burden is place upon the examiner. This is not found persuasive because the restriction requirement is based on lack of unity wherein the criterion is unity of invention. The scope of the composition is broader in scope than the method, and the groups do not have unity of invention for reasons set forth in the previous Office action. Accordingly, claims 1-13 are withdrawn from prosecution. Claim 14 and newly submitted dependent claims 15-18 are under examination.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The abstract of the disclosure is objected to because throughout the specification, reference is made to "claim 1." In the course of prosecution, claims are typically amended or canceled, so that a reference to claim 1 in an application may be rendered meaningless by the time the application is passed to allowance. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites the "production of a solid pharmaceutical preparation . . . which active substance is present in the form of a nanosol . . ." Applicant's definition of nanosol is "a stable colloidal disperse system of poorly water-soluble inorganic and/or organic compounds." This would suggest that the final product is in the form of a colloid, solid particles dispersed in liquid. However, step d) indicates drying the sol which appears to be at odds with the production of a colloidal product. Further regarding claim 14, as discussed above, the active substance is in the form of a "nanosol," but steps b)-d) recite a "sol." It is not clear if there any difference between a "sol" and a "nanosol," as recited. The difference in terminology renders the claims vague and indefinite.

Further regarding claim 18, the claim recites, "wherein a further polymeric carrier substance is used *apart from the chitosan derivative.*" (emphasis added) It is unclear how this polymeric carrier is to be used, thus rendering the claim vague and indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over ILLUM (US 5,863,554) and WUNDERLICH et al (US 5,932,245) in view of ROY et al (US 5,972,707).

The claims are drawn to a method for the production of a pharmaceutical preparation comprising a charged active substance in combination with an oppositely charged chitosan, wherein the preparation is in the form of a nanosol.

ILLUM teaches a drug delivery system comprising microspheres of gelatin or chitosan. See col 7. The reference suggests the use of a charged, poorly soluble active agent, such as indomethacin. See col 9, lines 33-40. The reference further suggests the use of a variety of agents with problematic availability. See col 8-9. The microspheres have utility in various modes of administration, such as gastrointestinal, nasal, etc. See col 5, lines 6-11. The reference does not teach the preparation of a nanosol.

WUNDERLICH teaches the preparation of nanosols by providing a gelatin and combining it with an oppositely charged active substance in an aqueous solution at a pH such that an isoionic state results. See abstract; col 7, lines 11-28; and examples. The reference further teaches the use of poorly water-soluble substances such as indomethacin. A solid product is prepared by drying techniques, such as freeze-drying or spray-drying, to prepare nanoparticles in the range of about 10-800 nm. See col 11, lines 14-33. The reference further teaches the addition of a polymeric auxiliary for the preparation of pharmaceutical compositions. See col 6, lines 28-37.

ROY teaches that both gelatin and chitosan are capable of forming nanoparticles in combination with an oppositely charged active agent. See example 3. Although ROY exemplifies

only the delivery of nucleic acids, the reference clearly recognizes the possibility of delivering agents to a variety of bodily targets by a variety of administration methods by varying the particle size. See paragraph bridging col 6 and 7. The reference further teaches that chitosan nanospheres can be prepared with a lower concentration of chitosan than the concentration needed for gelatin, and they are more stable than ones prepared with gelatin. See col 7, lines 24-34.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a solid pharmaceutical composition in the form of a nanosol comprising chitosan and an oppositely charged active agent by the method recited in claim 14. ILLUM had taught that chitosan and gelatin are functional equivalents in the delivery of therapeutic agents having problematic availability. The preparation method taught by WUNDERLICH comprising having the components at the isoionic point to produce a nanosol results in a product that is more stable. One of ordinary skill would reasonably expect success in using the WUNDERLICH process to prepare nanosols using chitosan because ROY had demonstrated that chitosan is at least equivalent to, if not superior to gelatin for the preparation of nanospheres in combination with an oppositely charged active agent. It would be further obvious to add an additional polymeric substance as an auxiliary for the preparation of a pharmaceutical formulation as taught by WUNDERLICH.

Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over ILLUM (US 5,863,554) and WUNDERLICH et al (US 5,932,245) in view of ROY et al (US 5,972,707)

and further in view of SHINETSU (JP 6-211903). Because the SHINETSU reference is in Japanese, the examiner is relying in part on the Derwent abstract.

The invention is as set forth above. Claim 15 recites the use of a positively charged active ingredient and a zwitterionic, acidic chitosan derivative.

ILLUM teaches as set forth above.

WUNDERLICH teaches as set forth above. The reference further teaches that two different types of gelatin may be used for the preparation of nanosols. One species of gelatin is Type B, which is alkaline and useful as a carrier for negatively charged active agents. This type of gelatin would be comparable to underivatized chitosan with respect to the type of active agent with which it could be combined for the preparation of a nanosol. Another species of gelatin is Type A, which is acidic and useful as a carrier for positively charged active agents. See Fig. 1.

ROY teaches as set forth above.

The combination of references does not teach the use of a zwitterionic, acidic chitosan derivative in combination with a positively charged active agent.

SHINETSU teaches the preparation of sulfated chitosan, a zwitterionic acidic chitosan derivative. The reference teaches that this chitosan derivative has utility as a drug carrier. See abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a solid pharmaceutical composition in the form of a nanosol comprising sulfated chitosan and an oppositely charged active agent by the method recited in claim 14. ILLUM had taught that chitosan and gelatin are functional equivalents in the delivery of therapeutic agents having problematic availability, and SHINETSU had taught that sulfated

chitosan also have utility in drug delivery. One of ordinary skill would reasonably expect success in using the WUNDERLICH process to prepare nanosols using sulfated chitosan for the preparation of nanospheres in combination with a positively charged active agent for reasons set forth above with regard to underivatized chitosan above.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Wednesday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-4624, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
February 3, 2004